

Attorney Docket No.: **P-457 (TI-0018)**  
Inventors: **Gjerde et al.**  
Serial No.: **09/826,055**  
Filing Date: **April 3, 2001**  
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#### **REMARKS**

The Examiner has indicated that claims 34-73 are pending. However, claims 34-47, 52-65 and 68-73 have been withdrawn from consideration. Applicants herewith cancel claims 34-47, 52-65 and 68-73. Accordingly, claims 48-51 and 66-67 are pending in this application. No new matter has been added. Reconsideration is respectfully requested in light of these amendments and the following remarks.

#### **I. Election/ Restriction**

The Examiner has deemed the restriction requirement mailed May 27, 2003 final. Claims 34-47, 52-65, and 68-73 have been withdrawn from consideration in this application.

In accordance with the making final of the restriction requirement dated May 27, 2003, please cancel claims 34-47, 52-65, and 68-73. Applicants reserve the right to pursue any or all subject matter set forth in claims 34-47, 52-65, and 68-73 in a divisional application(s).



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## **II A-B. Rejection of Claims under 35 U.S.C. § 103(a)**

### **A. Claims 48-50, 66 and 67**

Claims 48-50, 66 and 67 have been rejected under 35 U.S.C. § 103(a) over Oefner et al. (Analytical Biochemistry (1994) Vol. 223, pages 001-008) in view of Glazer et al. (U.S. Patent 5,763,162).

The Examiner suggests that Oefner teach a method of detection of polynucleotide separation by reverse phase ion pairing chromatography by contacting polynucleotides with dye; then applying to separation medium having nonpolar surface which is substantially free of multivalent cations; eluting the complex with mobile phase containing counterion agent and organic solvent; and detecting. The Examiner acknowledges that Oefner et al. do not teach any reversible DNA binding dyes.

Glazer et al. is suggested to teach the use of reversible intercalating dyes such as ethidium dimer in detecting DNA in separation methods including HPLC.

The Examiner suggests that one of skill in the art would have been motivated to apply Glazer et al.'s intercalating dyes to Oefner et al.'s separation technique in order to increase the level of fluorescent efficiency. Glazer et al. states that as



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opposed to covalent binding of dyes, intercalating dyes minimize self quenching and provide for high fluorescence efficiency. It is suggested to have been *prima facie* obvious to apply Glazer et al.'s intercalating dyes to Oefner et al.'s reverse phase chromatography method to increase the fluorescent emission for detection.

Applicants respectfully disagree with this rejection.

Under MPEP 706.02, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).



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First, it is only with Applicants' disclosure in hand that one of skill would be motivated to combine the recited references. Such a combination is impermissible hindsight.

Further, Glazer is not a proper prior art reference under MPEP section 102 or 103. The present application claims the benefit of priority dates including October 9, 1997; October 31, 1997; and February 24, 1998, all of which are earlier than the effective date of Glazer. Thus, Glazer may not be properly combined with Oefner under 35 U.S.C. 103(a).

The Examiner has acknowledged, *supra*, that Oefner alone does not disclose the claimed invention, in that Oefner simply teaches a method of separation by reverse phase ion pairing, Oefner does not teach or suggest reversible DNA binding dyes as useful in reverse phase ion pairing chromatography. At the time of filing, one of skill would not have been motivated to use a reversible intercalating dyes in Oefner's chromatography method. Thus, the instant invention cannot be deemed obvious in view of Oefner alone.

Accordingly, withdrawal of this rejection is respectfully requested.



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**B. Claim 51**

Claim 51 is rejected under 35 U.S.C. 103(a) as being obvious over Oefner et al. (Analytical Biochemistry (1994) Vol. 223, pages 001-008) in view of Glazer et al. (U.S. Patent 5,763,162, June 9, 1998) and further in view of Haugland (Handbook of Fluorescent probes and Research Chemicals, pages 221-229, 1994).

Haugland is suggested to teach the use of acridine orange and ethidium bromide. It is suggested that one of ordinary skill in the art would have been motivated to apply Haugland's acridine orange or ethidium bromide to the combined detection method of Oefner et al., and Glazer et al., in order to measure both double stranded DNA and RNA for diagnosis. Haugland is suggested to state that the dyes offer very versatile and popular stains for detecting nucleic acids. It is suggested that it would have been *prima facie* obvious to apply the acridine orange or ethidium bromide to the DNA in Oefner and Glazer's chromatographic method because the dyes were well known to provide successful and specific excitation maxima for the efficient detection of DNA.

Applicants respectfully disagree with this rejection.

First, as set forth above in detail, Glazer et al. is not a proper prior art reference under MPEP section 102 or 103. Thus,



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Glazer et al. may not be properly combined with Oefner or Haugland, under 35 U.S.C. 103(a).

Oefner alone does not disclose the claimed invention. As acknowledged by the Examiner, Oefner teaches a only method of separation by reverse phase ion pairing. Oefner does not teach or suggest reversible DNA binding dyes as useful in reverse phase ion pairing chromatography. Haugland is a handbook reference teaches membrane permeant dyes for use in cell staining. Haugland fails to supply or suggest the requisite teaching to disclose the present invention in view of Oefner. There is no teaching or suggestion in Haugland that reversible intercalating dyes are useful in detecting DNA in reverse phase ion pairing chromatography methods. Further, Haugland does not teach the use of reversible DNA-binding dyes or of DNA groove binding dye as required by claim 51. Further, Haugland makes no reference to PICO GREEN, propidium iodide, 7-aminoactinomycin D, cyanine dye, Bisbenzimidazole, Benzoxanthene yellow, Netropsin, Indole dye, Imidazole dye, or Actinomycin D, as recited in claim 51. Haugland teaches the use acridine orange and ethidium bromide as cell-permeant nucleic acid stains, see page 221, column 2 through page 222, column 1. Further, in contrast to the Examiner's



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suggestion, Haugland teaches that ethidium bromide is considered to be less sensitive than other dimers for detecting DNA in solution, see page 225, lines 7-9.

At the time of filing and in view of the available prior art, one of skill would not have been motivated to substitute a reversible intercalating dye in Oefner's chromatography method. Thus, claim 51 of the instant invention cannot be deemed to be obvious in view of the teachings of Oefner or Haugland, either alone or combined.

Accordingly, withdrawal of this rejection is respectfully requested.

#### **Conclusion**

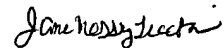
Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,



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favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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